REMARKS

Claims 1, 26, 28, and 53 are pending in the present application.

Claims 2-25, 27, and 29-52 have been cancelled without prejudice.

Claim 1 has been amended to specify that the immune response elicited by the composition is a cytotoxic T-lymphocyte response against tumor cells when orally administered to a patient. Support can be found in the working examples, e.g., in Examples 17-19 on pages 44-47. No new matter is introduced by this amendment.

Prior Rejections.

Applicants gratefully acknowledge that the prior new matter rejection has been withdrawn.

Rejections Under 35 U.S.C. §103(a).

Claim 1 stands rejected as allegedly being obvious under 35 U.S.C. §103(a) over the combination of Rovero *et al.* in view of Gordan *et al.*, Nagira *et al.*, and Lu *et al.* Claim 26 stands rejected over the same references as claim 1 and further in view of Bennet *et al.* Claim 28 stands rejected over the same references as claim 1 and further in view of Tanabe *et al.* Claim 53 stands rejected over the same references as claim 1 and further in view of Bennett *et al.* and Tanabe *et al.* These rejections are unwarranted.

The present Office Action maintains the obviousness rejections from the prior Office Action, alleging that it would have been obvious to one of ordinary skill in the art to have replaced the DNA encoding Her-2/neu antigen of the Rovero vaccine with DNA encoding survivin, based on the teachings of Gordan *et al.* (i.e., that survivin is a desirable target for anti-cancer therapy). The Office Action also asserts that one of ordinary skill in the art would have been motivated to replace the IL-1β DNA of the Rovero vaccine with CCL21 DNA, based on the teachings of Nagira *et al.* regarding the immune stimulating ability of CCL21 for attracting B and T cells, and that one of ordinary skill in the art would have been motivated to incorporate the so-modified Rovero vaccine in an attenuated *Salmonella typhimurium* vector based on the teachings of Lu *et al.*

Applicants maintain that the rejections amount to an impermissible *de novo* rebuilding of the Rovero vaccine utilizing survivin DNA and CCL21 DNA in an attenuated

Salmonella typhimurium vector based on the contention that it would have been obvious to do so due to the reported biological properties of the various components. This is, indeed, nothing more than an improper application the "obvious to try" standard. The Supreme Court's discussion of when the "obvious to try" rejection might be applied hinges on the accessability of a finite number of identified, predictable solutions, See *KSR Int'l Co. v. Teleflex Inc.* 127 S. Ct. 1727 (2007). That is not the case here, however.

The present invention does not represent a *predictable* variation of known elements or techniques in prior arts or fields of endeavor. The DNA vaccines of the present invention can be characterized as a novel form of "gene therapy" in that the vaccine must transfect antigen presenting cells (APC) in order to elicit an immune response. This is a very unpredictable field. For *prima facie* obviousness, there must be a reasonable expectation of success that the proposed combination will work. This presupposes that the skilled person is capable of rationally predicting, on the basis of existing knowledge, the successful conclusion of the subject invention without undue experimentation. The more unexplored a technical field of research is, the more difficult it is to make predictions about the likelihood of success. The present rejection simply presupposes, without any basis in fact, too much knowledge and predictability on the part of the person of ordinary skill and the field of endeavor, and does so in a manner which is wholly inconsistent with the Examiner's prior position *vis-a-vis* the alleged lack of enablement of the prior claims, in which unpredictability of the art in the same field of endeavor was asserted.

In the present case, there are, in fact, many potential choices for the tumor antigen and for the selection of a cytokine adjuvant, coupled with the need to select a delivery vehicle that will be effective for both the tumor antigen and the cytokine. The selection of all of these variants based on the applied art clearly would have involved undue experimentation. See also *Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd.*, 83 USPQ2d 1169 (Fed. Cir. 2007) (no identification of a predictable solution where prior art discloses a broad selection of compounds). The characterization in the Office Action of the state of this art as including "a finite number" of tumor antigens and cytokines misses the point. The finite number of alternatives must be "predictable" solutions to the problem. See *Takeda,* 83 USPQ2d at 1176. The art of vaccines and gene therapy can hardly be considered predictable.

The principal reference, Rovero *et al.*, discloses a plasmid DNA vaccine (not a bacterial vector) encoding the tumor antigen Her-2/neu (not survivin) and an immunologically

active fragment of IL-1β (not CCL21). The reference reports that immunization with this vaccine elicited lymphocyte infiltration into the stroma surrounding the terminal ductal-lobular units (TDLU) and induction of antibodies against the Her-2/neu antigen (anti-p185neu), as well as delayed tumor appearance in mice, but did not induce significant cytotoxic T lymphocyte (CTL) response (see page 449, col. 2, last full paragraph). Rovero *et al.* also reported that a plasmid DNA encoding only the Her-2/neu antigen did not elicit any significant immune response in the same mouse model (*Id.*).

The Office Action noted that the claims did not specify that the vaccine induce a CTL response. The presently amended claims do specify that a CTL response is elicited against tumor cells, however, and the presently claimed vaccine does indeed induce activation of CTLs (i.e., CD8 T cells). The present application indicates that while a vaccine encoding only the survivin protein did induce some anti-tumor response, the claimed combination encoding both survivin and CCL21 was significantly more effective (see in particular the results described in Examples 4, 5, and 17, on pages 33-35 and 44-45, demonstrating significant CD8 T cell activation in mice treated with the claimed vaccines, and Examples 3, 8, and 15, on pages 31-33, 36-37, and 41-43). These results show that the presently claimed vaccines operate by a significantly different immunological mechanism, i.e., via cellular immunity (CTL activation). The vaccines of Rovero *et al.* on the other hand, appear to invoke only humoral immunity (antibody production), a different immunological mechanism. There is nothing in the teachings of Rovero *et al.* either alone or in combination with the other applied references, that would have led one or ordinary skill in the art to reasonably expect such a CTL response to be induced. Indeed, the opposite result would have been reasonably expected.

As noted in the previous response, the immune system is complex and unpredictable. In order to be effective, immune system cells (e.g., B cells, Th cells, and/or CTLs) must migrate to, and infiltrate the tumor site. Nagira *et al.*, while providing general statements about the utility of a particular antigen or cytokine, provide little more than an invitation to experiment, but do not provide to one of ordinary skill a reasonable expectation that modifying a vaccine such as that of Rovero *et al.* by replacing the antigen target as well as the immunostimulating cytokine would successfully induce the required CTL response against tumor cells. This is particularly evident in the present case, where more than one factor is being altered in the primary reference at the same time, and the mechanism of the immune

response is dramatically different.

Obviousness must be assessed on the claimed invention as a whole. *Stratoflex, Inc. v. Aeroquip Corp.*, 218 USPQ 871 (Fed. Cir. 1983); M.P.E.P. 2141.02. One of ordinary skill in the art would not have had a reasonable expectation that the numerous modifications of the Rovero vaccine required by the present rejection would have successfully induced the required CTL response. As noted in the prior response, developing the presently claimed invention from the applied prior art would have required one of ordinary skill in the art to select survivin from a very large number of known tumor-associated antigens, and CCL21 from a large number of adjuvants that can enhance immune response, as well as also selecting an entirely different vector (i.e., the presently claimed *S. typhimurium* vector) from a multitude of available vectors to replace the plasmid of the Rovero vaccine. All of these selections being performed in an unpredictable art. Thus, many combinations and permutations of antigen, adjuvant and vector would have had to be constructed and tested in numerous tumor models to finally arrive at a product that successfully produced the required anti-tumor CTL response. Such a scenario clearly involves the kind of undue experimentation that mitigates against a finding of obviousness.

The prior art does not provide a predictable road-map to combine all of the elements of the present claims together to achieve the required CTL response without undue experimentation. The only road-map to the presently claimed invention of record here is the present application, itself. Hindsight use of the teachings of the application as a guide for combining all of the elements of the claims clearly is improper. *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988).

Unexpected Results.

Regardless of whether or not a *prima facie* case for obviousness has been established, the present invention provides benefits and results that are unexpected and could not have been predicted based on the teachings of the prior art. For example, the data in Table 2, on page 35, clearly demonstrate a significant upregulation of CD8 T-cells that express CD25, CD28 and CD69 activation markers, in comparison to examples involving only the survivin protein or only the CCL21. These increased expression levels would not have been predictable from the allied prior art, i.e., Nagira *et al.*, which does not disclose or even suggest the enhanced expression of these T-cell markers by CCL21.

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As a further example, the data in Table 3, on page 42, clearly indicates a dramatic reduction in D121 Lewis lung tumor metastasis in mice vaccinated with the claimed vaccine relative to mice treated with a vaccine comprising survivin DNA alone or CCL21 DNA alone, i.e., 6 out or 8 mice treated with the claimed virus had metastasis scores of "0". The remaining mice had scores of "1", compared to the results from mice from the survivin or CCL21 treatment groups, in which the majority of mice had metastasis scores of "2" or "3". The prior art simply does not provide sufficient information for one of ordinary skill to have predicted these improvements demonstrated by the present invention. Accordingly, the obviousness rejection should not be maintained.

Conclusion.

In view of the foregoing, Applicants request reconsideration, allowance of the present claims, and early passage of the application to issue. In the event the foregoing is deemed unpersuasive, Applicants request entry of the present amendment to place the claims in better form for appeal.

Respectfully submitted,

Dated January 22, 2009 By _____
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